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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,928	10/05/1998	NORIO INOMATA	001560-336	8658

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	31

DATE MAILED: 08/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/171,928	INOMATA ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8-11 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued examination under 37 CFR 1.114 after final rejection

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/09/2003 has been entered.

Status of Claims

2. Claims 8-11,21 are currently pending.

Claim Rejections - 35 USC § 112, first paragraph.

3. Claims 8-11,21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims as amended introduce new matter in claiming treatment of heart failure by reducing pulmonary congestion. The disclosure is drawn to treatment of heart diseases caused by cardiac

hypertrophy (p. 4, lines 27,28). The specification does not teach treatment of heart diseases caused by pulmonary congestion. Rather, the specification addresses that in the animal model studied pulmonary congestion happens to be a "major symptom of heart failure" (p. 9, lines 19-21). Similarly, prior art, such as Tilley et al. (Recent advances in studies on cardiac structure and metabolism, (1975) 10, 641-53, see abstract) addresses pulmonary congestion as clinical manifestation rather than a cause of heart failure. There is no nexus between the observed effects on pulmonary congestion and heart failure.

4. Claims 8-11,21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing cardiac hypertrophy is rats using ANP at dosages which do not cause hypertensive or diuretic effect, does not reasonably provide enablement for (1) treatment of cardiac hypertrophy with ANP in species other than rats at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with agents other than ANP and at dosages which do not cause diuretic and hypotensive effects.

The specification is limited to demonstration of one agent (ANP) and in one type of species (rats). In regard to (1) use in humans, applicants speculate that the data on rats can be extrapolated to other species. There is no support that (I) mechanisms

of the effect of ANP, namely acting without causing diuretic and hypotensive effects, and (ii) sensitivity of receptors to ANP, are the same in rats in humans. Applicants argue in their responses that the finding of the effect of ANP without involving hypotensive and diuretic effect is unexpected and unusual, the art in this regard is deemed unpredictable, and it is not clear whether such effect observed in rats will be similarly manifested in other mammalian species.

In regard to (2), again, as applicants argue in their responses that the finding of the effect of ANP without involving hypotensive and diuretic effect is unexpected and unusual, the art in this regard is deemed unpredictable, and it is not clear whether other agents will have same specific mechanism of action.

Response to arguments

Applicants argue that showing of effect of ANP in rats is sufficient to enable to enable the full scope of the claims. Examiner disagrees. References discussed by applicant on pages 4,5 of the response do not provide any evidence that ANP or similar agents have identical mechanisms of action in rats and other mammalian species, and/or that sensitivity of receptors to ANP is the same in rats in humans. Consequently, Examiner maintains that the art is deemed unpredictable in regard to ANP acting without involving hypotensive and diuretic effects, and, in the absence or

working examples and sufficient guidance, specification does not commensurate with the scope of invention claimed.

Claim Rejections - 35 U.S.C. § 102 and 103.

5. Claims 8-11,21 are rejected under 35 U.S.C. 103(a) as obvious over Blaine or Berman in view of Cao et al. and Espiner[1].

Blaine teaches method of treatment of cardiac hypertrophy using atrial natriuretic peptide (ANP) and fragments thereof. See abstract, summary, claims 1-8.

Berman et al. teach treatment of cardiac hypertrophy using atrial natriuretic peptide (ANP) analogues which bind to natriuretic receptor. See abstract.

The referenced methods read on a method of treatment of heart disease based on hypertrophy comprising administration of a substance that acts on natriuretic receptor, guanylyl cyclase A and is able to accelerate production of cGMP. Note, that it is well known that ANP, as well as its analogs stimulate guanylate cyclase A and production of cGMP. See Espiner, p. 205, last paragraph.

The referenced methods do not teach treatment of pulmonary congestion. However, it would be prima facie obvious to one skilled in the art at the time the

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[1]Note that, although the date of the "Espiner" reference is later than the priority date of the instant application, the reference is a review describing studies preceding the instant application; the reference is used merely to demonstrate well known mechanisms of action.

invention was made that treatment of cardiac hypertrophy will alleviate heart diseases caused by cardiac hypertrophy, primarily cardiac failure. Consequently, it would be obvious that treatment of cardiac hypertrophy will alleviate pulmonary congestion which is well known to be a clinical manifestation of cardiac failure (see, for example, Tilley et al. (Recent advances in studies on cardiac structure and metabolism, (1975) 10, 641-53, see abstract)).

In regard to the instant claims limitation "amount... not effective for diuretic and hypertensive effects", the references are silent about the presence of such effects of ANP. Although Blain demonstrates reduction in water content, such demonstration, as discussed in the preceding Office actions, does not amount to demonstration of a diuretic effect. Note that prior art acknowledges that, first, natriuretic peptides have a wide range of actions, and, second, hypertrophy is a result of an interaction between a variety of different interrelated signaling pathways. See, for example, Espiner, p. 205, right column, lines 30-33. Therefore, it is not possible to discern which particular mechanism was engaged in achieving an overall effect of treatment. Even though separate mechanisms might have been discerned in specifically designed model conditions, Examiner assumes that in the referenced methods ANP exerts the effect as instantly claimed. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on

applicant to show that the referenced method did not include the effect as instantly claimed.

Further, even though the primary references do not teach that the reduction of heart weight achieved as a result of the treatment excludes, specifically, such mechanisms as diuretic or hypotensive effects, the involvement of effects other than diuretic or hypotensive would be obvious from the prior art. Thus, Cao et al teaches that (1) cardiac hypertrophy include stimulation of gene cascade; (2) natriuretic peptides reduce stimulation of this cascade, as evidenced by a decrease in thymidine incorporation (the reference suggests that "such growth-suppressing activity raise the intriguing possibility that [natriuretic peptides] may function in paracrine fashion to modulate growth in the interstitial compartment during cardiac hypertrophy; see p. 227, bottom); (3) demonstrates that the hypertrophy-reducing effect of the natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and is further mediated by formation of cGMP (p. 231, and p. 233, second paragraph. Therefore, it would be obvious to one skilled in the art that cardiac hypertrophy can be reduced by natriuretic peptides by interference with gene activation and that the effect of treating cardiac hypertrophy described in the referenced methods might have included the mechanism as instantly claimed.

In regard to claim 7, chronic heart failure is a disease based on cardiac hypertrophy.

In regard to claim 10, Espiner teaches that BNP is a functional equivalent of ANP. See p. 205, right column through p. 206, left column.

In regard to claim 11, if there are any differences between Applicant's claimed methods and that of the prior art, the differences would be appear minor in nature. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ways of administration and pharmaceutical carriers as they are art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art.

Response to arguments

Applicant addresses all references in a similar fashion arguing that the reference do not mention reduction of pulmonary congestion and thus treatment of heart failure. However, the instant disclosure does not teach such causative effect (see new matter rejection under 35 U.S.C. 112, first paragraph). The disclosure is drawn to treatment of heart diseases caused by cardiac hypertrophy (p. 4, lines 27,28). The specification does not teach treatment of heart diseases caused by pulmonary congestion. Rather, the specification addresses that in the animal model studied pulmonary congestion

happens to be a "major symptom of heart failure" (p. 9, lines 19-21). Similarly, prior art, such as Tilley et al. (Recent advances in studies on cardiac structure and metabolism, (1975) 10, 641-53, see abstract) addresses pulmonary congestion as clinical manifestation rather than a cause of heart failure. Thus, as there is no nexus between the observed effects on pulmonary congestion and heart failure, the claimed method is addressed in the art rejection as method of treatment of heart hypertrophy, and thus, consequently, method of treatment of heart failure and its clinical manifestation, pulmonary congestion.

Conclusion.

6. No claims are allowed

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael Borin

Primary Examiner